STRUCTURAL BIOLOGY OF MEMBRANE PROTEINS SBIR/STTR ANNOUNCEMENT

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APPLICATION RECEIPT DATES: April 1, August 1, December 1

EXPIRATION DATE: April 10, 2005 unless reissued

PARTICIPATING INSTITUTES AND CENTERS (ICs):

National Institute of General Medical Sciences (NIGMS)
(http://www.nigms.nih.gov/)
National Cancer Institute (NCI)
(http://www.nci.nih.gov/)
National Heart, Lung, and Blood Institute (NHLBI)
(http://www.nhlbi.nih.gov/)
National Institute on Aging (NIA)
(http://www.nia.nih.gov/)
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
(http://www.niams.nih.gov/)
National Institute on Deafness and Communication Disorders (NIDCD)
(http://www.nidcd.nih.gov/)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
(http://www.niddk.nih.gov/)
National Institute on Drug Abuse (NIDA)
(http://www.nida.nih.gov/)
National Institute of Environmental Health Sciences (NIEHS)
(http://www.niehs.nih.gov/)
National Institute of Mental Health (NIMH)
(http://www.nimh.nih.gov/)
National Institute of Neurological Disorders and Stroke (NINDS)
(http://www.ninds.nih.gov/)
National Center for Research Resources (NCRR)
(http://www.ncrr.nih.gov/)

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PURPOSE OF THIS PA

The purpose of this PA is to encourage researchers to solve the structures of membrane proteins at atomic resolution and to develop the tools needed to solve these structures. Considerable research on the structure and function of membrane proteins is under way. Yet, relatively few investigators use x-ray crystallography, electron diffraction, or nuclear magnetic resonance (NMR) spectroscopy to study the structures of these proteins directly. During the past decade, investigators have determined the structures of approximately 30 membrane proteins. The solution of each structure has been a major contribution to a particular area of science (see http://blanco.biomol.uci.edu/Membrane_Proteins_xtal.html). This progress clearly demonstrates that determining the structures of membrane proteins is feasible. However, the rate of solving soluble protein structures also has accelerated greatly during the past decade. Thus, a gap remains between understanding membrane proteins and understanding their soluble protein counterparts.

The National Institutes of Health (NIH) has undertaken the Protein Structure Initiative (PSI) to accelerate further the rate of solving protein structures. (See: http://www.nigms.nih.gov/funding/psi.html). Some PSI centers include efforts to determine the structures of membrane proteins, and the PAs for the PSI encourage the development of technologies for high-throughput approaches to determine the structures of these proteins (see http://grants.nih.gov/grants/guide/pa-files/PA-99-116.html). Nonetheless, a separate program initiative is needed to focus primarily on membrane proteins and the development of methods for

solving their structures. An increase in the number of known membrane protein structures will help to enhance understanding of many basic phenomena underlying the cellular functions essential to human health and may lead directly to products that have commercial value and societal impact.

This PA is offered through the NIH Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grant program and is directed to eligible small businesses. A parallel PA, Structural Biology of Membrane Proteins (PA-02-060), offers support for applicants other than small businesses to conduct investigator-initiated (R01) research of identical technical and scientific scope (see http://grants.nih.gov/grants/guide/pa-files/PA-02-060.html and addendum http://grants.nih.gov/grants/guide/notice-files/NOT-DA-02-004.html).

RESEARCH OBJECTIVES

Membrane proteins have a crucial role in many cellular and physiological processes. They are essential mediators of the transfer of material and information between cells and their environment, between compartments within cells, and between compartments of organ systems. Membrane proteins that function normally are vital to health, and specific defects are associated with many known disease states. Membrane proteins are the targets of many pharmacologically and toxicologically active substances and are responsible, in part, for the uptake, metabolism, and clearance of these substances.

Membrane proteins are thus commercially important. Knowledge of the structure of a particular membrane protein may be commercially valuable in itself or may lead to the development of commercially valuable agonists, antagonists, or inhibitors. Research tools that can help researchers in academic laboratories solve the structure of membrane proteins occupy a niche market, but may be commercially viable and would have significant societal impact by contributing to the overall NIH effort to stimulate research on the structure of membrane proteins.

Despite the importance of membrane proteins, knowledge of their high resolution structures and mechanisms of action has lagged far behind the knowledge of these properties of proteins in general. This gap in understanding has resulted from the difficulties of obtaining x-ray-diffraction-quality crystals for membrane proteins and of applying well-developed solution NMR methods to the study of most membrane proteins. Because of these difficulties, many investigators have been reluctant to pursue high-resolution studies of the structures of membrane proteins.

Recently, however, advances in crystallization and analysis of proteins by x-ray and electron diffraction and improvements in NMR methods offer new opportunities. Further, the solution of crystal structures, after suitable crystals are obtained, has, in many cases, become sufficiently routine that crystallization itself is often the more major undertaking. For this PA, therefore, protein production, protein crystallization, and the solution of protein structures are all worthy aims.

The specific objectives of this PA are to encourage small businesses to:

1) Undertake the challenge of solving the structures of membrane proteins, and

2) Further develop methods and reagents for studying the structures of membrane proteins at atomic resolution.

Examples of methods that need specific attention include, but are not limited, to methods for:

o Overexpression of native and modified membrane proteins

o Isolation, purification, and stabilization of membrane proteins, including development of new detergents and non-detergent solubilization agents

o Crystallization of membrane proteins and crystal manipulation that could facilitate data collection

o Electron diffraction, particularly for the production of suitable two-dimensional crystals

o NMR analysis of membrane proteins in solution, micelles, and their native lipid environments

o Elucidating the organization of lipid and detergent molecules within protein crystalline arrays (e.g., neutron diffraction).

This PA emphasizes x-ray or electron diffraction and NMR spectroscopy because these techniques currently show the most promise for producing the most complete high-resolution information for the largest number of proteins. However, we are also interested in other methods that can provide atomic-resolution information in selected cases.

Much of the research in this area is likely to be collaborative efforts between biochemists and molecular biologists, with expertise in the isolation and characterization of membrane-bound proteins, and biophysicists, with expertise in x-ray crystallography, NMR, and other structural methods. A major aim of this PA is to stimulate these collaborations.

Listed below are examples of the types of membrane protein systems that are of particular interest to the participating institutes:

NIGMS: Energy transducing membranes of mitochondria, chloroplasts, and bacterial cell membranes involved in electron transport and ATP synthesis; channels, pores, and transporters of ions, substrates, and macromolecules between intracellular compartments and between the cell and its environment; enzymes in the synthesis and metabolism of lipids, membrane-associated and secreted proteins, and glycoconjugates; cytoskeletal proteins, including those required for intracellular vesicle transport, cell motility, and cell division; regulators of cell-cell communication, differentiation, and growth; receptors relevant to cell-cycle regulation, mechanisms of anesthetic action, and trauma and burn physiology; transporters and enzymes responsible for the uptake, metabolism, and clearance of drugs or other effects on the bioavailability, pharmacokinetics, or action of drugs; targets of drug action and toxicity, including targets of naturally occurring toxins and venoms; and enzymes involved in the biosynthesis of natural products.

NCI: Membrane proteins and membrane complexes associated with the biology, diagnosis and treatment of cancer. These include membrane proteins whose alterations have been linked to the development and progression of cancer or that are part of cancer-related signaling pathways; proteins associated with the extracellular matrix (for example, laminins and fibronectin); and proteins with potential as diagnostic markers and/or therapeutic targets. NCI is also soliciting applications focused on the development of new approaches and technologies for the isolation, purification, and structure determination of these proteins. Applicants strictly focused on technology may wish to consider applying under the NCI Innovative Molecular Applications of Technology Program (see http://otir.nci.nih.gov/tech/funding.html).

NIAMS: Membrane protein systems with specific relevance to muscle function and disease; bone and cartilage function and disease; and skin function and disease. Examples include: membrane proteins involved in excitation, relaxation, force transduction, cellular homeostasis, and metabolism; regulators of cell-cell communication and attachment (e.g., costameres, myotendinous and neuromuscular junctions); ion channels, receptors, transporters, and enzymes that affect the function and hypertrophy or atrophy of muscles; membrane proteins of skin

involved in establishment of the stratum corneum barrier, epidermal cell-cell attachment and communication, transmembrane signaling and transport, and cell movement, including genetic and acquired diseases of the skin in which the membrane protein is defective or targeted (which may encompass both benign and malignant hyperproliferative diseases).

NIDA: Receptors and transporters relevant to drug abuse research. These proteins include: the cannabinoid CB1 and CB2 receptors; the vanilloid receptor; the orphanin receptor; the mu, delta, and kappa opioid receptors; the neuronal nicotinic receptor subtypes; the NMDA receptor complex; the metabotropic glutamate receptors I-III; the GABA-A receptor; the dopamine, serotonin, and norepinephrine transporters; and any other neuropeptide receptors that are affected by drugs of abuse.

NIDCD: Membrane proteins involved in the auditory, vestibular, olfactory, taste, voice, speech and language sensory systems. Eukaryotic proteins of interest include: transporters, ion channels, ligand receptors, G-protein coupled receptors, transcription and associated factors, motor and motor associated proteins, growth factor receptors, and cytoskeletal structural components involved in the function of these sensory and neural functions. Prokaryotic membrane proteins of interest include: proteins from numerous viral and microbial organisms involved in otitis media or serving as identifiable markers (such as muscin)for middle ear infections.

NIDDK: Membrane protein systems with specific relevance to diseases of transport, such as cystic fibrosis and peroxisomal biogenesis disorders; carbohydrate metabolism and its hormonal control; diabetes mellitus; hormone receptors and signal transduction; endocrine disorders; normal and abnormal processes of lipid, protein, amino acid, urea, pyrimidine, metal ion, and steroid metabolism; and genetic metabolic disorders. Proteins should be of mammalian origin. Studies of proteins of prokaryotic or lower eukaryotic origin should be proposed as models for mammalian systems. An example is the ATP Binding Cassette transporter superfamily or traffic ATPases in bacteria and yeast, which serve as models for the cystic fibrosis transmembrane regulator (CFTR).

NIEHS: Membrane proteins and enzymes involved in the response of cells to environmental toxicants. These proteins and enzymes may include the components of the stress signaling pathway or ion channels involved in the transport of xenobiotics (e.g., membrane transporters such as PgP, MDR, and MRP2); transporters and enzymes responsible for the uptake and clearance of environmental toxicants; targets of toxicant action, including the Ah receptor and

non-classical receptors for endocrine-disrupting agents; and membrane-bound heat shock proteins.

NIA, NIMH, and NINDS: Neurotransmitter and growth factor receptors, transporters, ion pumps, voltage- and ligand-gated ion channels (e.g., those involved in channelopathy), trafficking proteins, mitochondrial proteins, structural proteins and other proteins involved in the normal function and pathology of cells (neurons and glia) in the central and peripheral nervous systems. Also, proteins involved in synaptic transmission and in the regulation, metabolism, homeostasis, and signaling in the brain during functions such as learning, memory, or cognition, during development and aging into late-life, and in disorders of the central nervous system.

NCRR: The Biomedical Technology Division is interested the development of new technologies such as instrumentation and methodologies that will enhance the capacity to elucidate structures of membrane proteins.

SUMMARY

The purpose of this program announcement is to stimulate research leading to the solution of membrane protein structures at atomic resolution. The above lists of membrane proteins are not meant to be exclusive. Structural information obtained for any membrane protein will contribute to the understanding of general principles that underlie the structure and function of all membrane proteins. The participating institutes also support research on non-membrane proteins associated with many of the cellular functions listed above. However, this PA emphasizes the need for additional research on structural aspects of membrane proteins involved in these processes and the need to develop new tools to study membrane protein structures.

MECHANISM OF SUPPORT

This PA will use the SBIR (R43, R44) and STTR (R41, R42) award mechanisms, which are designed to encourage development of technology by eligible small businesses. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project. You should read this PA in conjunction with the "Omnibus Solicitation of the National Institutes of Health for Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Grant Applications", which describes the SBIR/STTR grant program (see http://grants.nih.gov/grants/funding/sbirsttr1/index.pdf).

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution is an eligible, domestic, for-profit small business organization, as described for SBIR and STTR grant applications in the Omnibus Solicitation. We encourage you to access this solicitation for information on eligibility requirements (see http://grants.nih.gov/grants/funding/sbirsttr1/index.pdf).

Eligibility for the parallel PA (Structural Biology of Membrane Proteins, PA-02-060) is broader and encompasses foreign and domestic, for-profit and non-profit, and public and private organizations, such as universities, colleges, hospitals, laboratories, companies, units of State and local governments, and eligible agencies of the Federal government. (See http://grants.nih.gov/grants/guide/pa-files/PA-02-060.html and addendum: http://grants.nih.gov/grants/guide/notice-files/NOT-DA-02-004.html).

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individuals with the skills, knowledge, and resources necessary to carry out the proposed research are invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

SPECIAL REQUIREMENTS

You are reminded that NIH policy requires the timely publication of structural study results and the deposition of atomic coordinates of solved protein structures into structural databases immediately upon publication of results (see http://grants.nih.gov/grants/guide/notice-files/not99-010.html).

WHERE TO SEND INQUIRIES

We encourage your inquiries concerning this PA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

o Direct your questions about scientific/research issues to:

Peter C. Preusch, Ph.D.
Division of Pharmacology, Physiology, and Biological Chemistry

National Institute of General Medical Sciences
45 Center Drive, MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-5938
FAX: (301) 480-2802
Email: preuschp@nigms.nih.gov

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6001 Executive Boulevard, Room 4282, MSC 9555
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Margaret C. Grabb, Ph.D.
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FAX: (301) 480-3659
Email: swaina@ncrr.nih.gov

o Direct your questions about peer review issues to:

Stephen M. Nigida, Jr., Ph.D.
Center for Scientific Review
Room 4212; MSC 7812
6701 Rockledge Drive
Bethesda, Maryland 20817
Telephone: (301) 435-1222
Fax: (301) 480-4042
Email: nigidas@csr.nih.gov

o Direct your questions about financial or grants management matters to:

Ms. Grace Tuanmu

Grants Administration Branch
National Institute of General Medical Sciences
45 Center Drive, MSC 6200
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Ms. Linda Whipp
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Mr. Michael Morse
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Mr. Paul Karadbil
Office of Grants Management
National Center for Research Resources
6705 Rockledge Drive, Room 6086
Bethesda, Maryland 20892-7965
Telephone: (301) 435-0844
FAX: (301) 480-3777
Email: paulk@ncrr.nih.gov

SUBMITTING AN APPLICATION

You may submit your application as a Phase I or Phase II application or as a Fast Track pair of Phase I and Phase II applications. See "Specific Instructions" below.

Applications must be prepared using the SBIR and STTR application instructions and forms. These are available at http://grants.nih.gov/grants/funding/sbir.htm in an interactive PDF format. The PDF files are hyperlinked as Appendices A through E subtopics under the SBIR/STTR Phase I Solicitation link.

APPLICATION RECEIPT DATES: Applications submitted in response to this PA will be accepted at the following application deadlines: April 1, August 1, and December 1.

SPECIFIC INSTRUCTIONS FOR PHASE I APPLICATIONS: Application forms, requirements, and procedures are the same as listed in the Omnibus Solicitation for Phase I SBIR/STTR Grant applications (http://grants.nih.gov/grants/funding/sbirsttr1/index.pdf), except for the following:

o Type the title and number of this PA on line 2 on the face page of the application.

o The Omnibus Solicitation states levels for Phase I and Phase II budgets that are guidelines, not ceilings. For this PA, we will consider larger budgets for longer periods of time, if they are well justified and necessary to complete the proposed research and development. Applications for $100,000 may be submitted in modular form. Applications for over $100,000 must include a detailed budget and budget justification.

SPECIFIC INSTRUCTIONS FOR Phase II Applications: We will only accept Phase II applications as competing continuations of previously funded NIH Phase I SBIR or STTR awards. The Phase II application must be for developmental work that is a logical extension of the feasibility research conducted during Phase I. When preparing an application for a Phase II award, you should follow the instructions for NIH Phase II SBIR or STTR applications. The instructions and forms for a Phase II SBIR and STTR award are available at http://grants.nih.gov/grants/funding/phs398/phs398.html.

SPECIFIC INSTRUCTIONS FOR Fast Track Applications: For Fast Track applications, the NIH expedites evaluation of progress following the Phase I feasibility study, for transition to the Phase II funding for expanded developmental work. You may request Fast Track review of your application. Information on this option is available at http://grants.nih.gov/grants/funding/sbirsttr1/index.pdf.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the checklist, and five signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

APPLICATION PROCESSING: Applications must be received by or mailed on or before the receipt dates noted above. The CSR will not accept any application in response to this PA that is essentially the same as one currently pending initial review unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.

PEER REVIEW PROCESS

Applications submitted for this PA will be assigned on the basis of established PHS referral guidelines. An appropriate scientific review group convened in accordance with the standard NIH peer review procedures (http://www.csr.nih.gov/refrev.htm) will evaluate applications for scientific and technical merit.

As part of the initial merit review, all applications will:

o Receive a written critique
o Undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
o Receive a second level review by the appropriate national advisory council or board

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of your application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

- Significance
- Approach
- Milestones and Proof of Principle
- Innovation
- Investigator
- Environment

The scientific review group will address and consider each of these criteria in assigning your application's overall score, weighting them as appropriate for each application. Your application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, you may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) SIGNIFICANCE: Does your study address an important problem? Does the proposed project have commercial potential to lead to a marketable product or process? What may be the anticipated commercial and societal benefits of the proposed activity? If the aims of your application are achieved, how do they advance scientific knowledge? Does the proposal lead to technologies (e.g., instrumentation, software) that will enable further discoveries? Will the technology have a competitive advantage over existing/alternate technologies that can meet market needs?

(2) APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Do you acknowledge potential problem areas and consider alternative tactics? What is the time frame for developing the proposed technologies, and is this time frame suitable for meeting the community's needs? How easy will it be to use the proposed technology? Are your plans adequate for the proposed technology, its integration as an effective solution for implementation, and dissemination? If you are proposing industrial partnerships, how will they facilitate the development and integration of system components?

(3) MILESTONES (for Phase I R41 or R43 or Fast Track applications) AND PROOF OF PRINCIPLE (for Phase II applications): If you are submitting a Phase I application, how appropriate are your proposed milestones for evaluating demonstration of feasibility for transition to the R42 or R44 Phase II development work? Do the milestones provide an objective target for evaluating results? If you are submitting a Phase II application, how well has the feasibility or proof of principle been demonstrated?

(4) INNOVATION: Does your project employ novel concepts, approaches, or methods? Are the aims original and innovative? Does your project challenge existing paradigms or develop new methodologies or technologies? What is the throughput and cost-effectiveness of your proposed technology? What additional uses can be projected for your proposed technology?

(5) INVESTIGATOR: Are you appropriately trained and well suited to direct this work? Is the work proposed appropriate to your experience level as the principal investigator and to that of other researchers (if any)?

(6) ENVIRONMENT: Is there sufficient access to resources (e.g., equipment, facilities)? Does the technical and scientific environment in which your work will be done contribute to the probability of success? Does the proposed work take advantage of unique features of the technical and scientific environment or employ useful collaborative arrangements?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, your application will also be reviewed with respect to the following:

PROTECTIONS: The adequacy of the proposed protection for humans, animals, or the environment, to the extent they may be adversely affected by the project proposed in the application.

INCLUSION: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

AWARD CRITERIA

Applications submitted in response to this PA will compete for available funds with all other recommended SBIR and STTR applications. The following will be considered in making funding decisions for Phase I or Phase II applications:

- Quality of the proposed project as determined by peer review
- Availability of funds
- Relevance to program priorities

Phase II applications will be selected for funding based on the following:

- Quality of the proposed project as determined by peer review
- Assessment of Phase I progress
- Determination that the Phase I goals were achieved
- The project's potential for commercial success
- Availability of funds

Fast Track Phase II applications may be funded following submission of:

- The Phase I progress report
- Other documents necessary for continuation

REQUIRED FEDERAL CITATIONS

It is not anticipated that proposals submitted in response to this PA will involve human subject studies.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data collected under SBIR and STTR grants are exempted. See: http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm).

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites.

Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance No. 93.113, 93,173, 93.242, 93.279, 93.371, 93.396, 93.821, 93.837, 93.846, 93.847, 93.853, 93.859, 93.866 and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (15 USC 638 and 42 USC 241 and 284) and administered under NIH grants policies described at http://grants.nih.gov/grants/policy/policy.htm and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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